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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	PAPER NUMBER
1637	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/747,538	Applicant(s) KATZ ET AL.	
	Examiner Suryaprabha Chunduru	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-37 are pending.

2. The disclosure is objected because of the following informalities:

The abstract of the disclosure is objected to because the abstract is too lengthy and exceeds more than 150 words. See MPEP § 608.01(f). it reads as follows:

Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims. In an international application which has entered the national stage (37 CFR 1.491(b)), the applicant need not submit an abstract commencing on a separate sheet if an abstract was published with the international application under PCT Article 21. The abstract that appears on the cover page of the pamphlet published by the International Bureau (IB) of the World Intellectual Property Organization (WIPO) is the abstract that will be used by the USPTO. See MPEP § 1893.03(e).

Correction is required accordingly.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

a. Claims 9, 23 and 35 recite the limitation "the" in patient's medical care regimen. There is insufficient antecedent basis for this limitation in the claim. The limitation "the" in the claim lacks definite basis. Though the specification does support the instant claim, the specification cannot be read into the instant claim. Amendment of the claim to clearly specify the patient's care regimen would obviate the rejection.

b. Claim 13 recites the limitation "the" in same apparatus. There is insufficient antecedent basis for this limitation in the claim. The limitation "the" in the claim lacks definite basis. Though the specification does support the instant claim, the specification cannot be read into the instant claim. Amendment of the claim to clearly specify the same apparatus would obviate the rejection.

c. Claims 9, 23, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

Method claims require a last step or phrase in the last step that states the accomplishment of the goals for the method, which were stated in the method's preamble. The instant claims lack such a last step (how an alteration of a patient's medical care regimen is determined/ or how the step of altering the patent's medical care regimen is achieved?) and is confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

a. Claims 1, 4-5, 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Johansson et al. (pharmacogenetics, vol. 6, pages 351-355, 1996).

Johansson et al. teach a method for distinguishing the presence of a target nucleic acid and a variant which comprises a deletion (deletion of entire coding region (CYP2D6*5)), wherein Johansson et al. disclose that the method comprises contacting a test sample (containing DNA) with amplification reagents and a first and second amplification primer specific for the target site, subjecting the reaction mixture to amplification conditions, and detecting the amplification product as an indication of the presence of the target nucleic acid sequence (see page 351, column 1, paragraph 1, and page 353, column 2, paragraph 1). Johansson et al. also teach that the method comprises (i) control nucleic acid and primers to amplify control nucleic acid sequences, which could be selected from the said first and second primers (see page 354, column 1, paragraph 2); (ii) failure to detect an amplification product is an indication of the presence of the variant (CYP2D6 gene deletion) in the sample (see page 354, column 1, paragraph 2). (iii) the method could be used to alter drug therapy (patient's care) and for evaluating the linkage between the CYP2D6 genotype and disease and aid in drug development

(see page 354, column 2, paragraph 1). Thus the disclosure of Johansson et al. meets the limitations in the instant claim.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

a. Claims 2-3, 6, 17-25, 28-32, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansson et al. (pharmacogenetics, vol. 6, pages 351-355, 1996) and in view of Jou et al. (WO 98/48052).

Johansson et al. teach a method for distinguishing the presence of a target nucleic acid and a variant which comprises a deletion (deletion of entire coding region (CYP2D6*5)), wherein Johansson et al. disclose that the method comprises contacting a test sample (containing DNA) with amplification reagents and a first and second amplification primer specific for the target site, subjecting the reaction mixture to amplification conditions, and detecting the

amplification product as an indication of the presence of the target nucleic acid sequence (see page 351, column 1, paragraph 1, and page 353, column 2, paragraph 1). Johansson et al. also teach that (i) the method comprises control nucleic acid and primers to amplify control nucleic acid sequences, which could be selected from the said first and second primers (see page 354, column 1, paragraph 2); (ii) failure to detect an amplification product is an indication of the presence of the variant (CYP2D6 gene deletion) in the sample (see page 354, column 1, paragraph 2); (iii) the method could be used to alter drug therapy (patient's care) and for evaluating the linkage between the CYP2D6 genotype and disease and aid in drug development (see page 354, column 2, paragraph 1). However, Johansson et al. did not teach detection of amplification product using probe(s) and amplification of control nucleic acid sequence.

With reference to the instant claims 2-3, Jou et al. teach a method for distinguishing the presence of a target nucleic acid sequence and a variant sequence in a test sample wherein Jou et al. disclose that the method comprises (i) contacting the test sample with amplification reagents and a first and second amplification primers, subjecting the reaction mixture to amplification conditions and detecting the amplification product as an indication of the target nucleic acid sequence in the test sample (see page 3, lines 16-31); (ii) detecting the presence of the amplification product by hybridizing a probe (labeled) to the amplification product (see page 3, lines 31-36, page 4, lines 1-7). And lack of detection of amplified product is an indication of the presence of the variant in the test sample (page 8, lines 1-11).

With reference to claims 17- 21, Jou et al. teach that said a method comprising contacting test sample (comprising normal and mutant sequences) with amplification reagents comprising a PCR primer pair(s), and a probe(s) and performing amplification (repeated denaturation,

annealing and primer extension steps) and detecting the amplification product as an indication of the nucleic acid sequence in the test sample (see page 9, lines 17-35, page 10, lines 1-2, page 11, lines 22-36, page 12, lines 1-22); Jou et al. also teach that amplification product could be detected in the presence of two probes a mutant probe and a wild type (control) probe, which can be labeled and attached to a solid support (see page 8, lines 17-33, page 7, lines 3-13) and distinguishing or comparing signals for a mutant and normal alleles in the test sample (see page 9, lines 1-16, page 20, lines 22-28, page 21, lines 1-17);

With reference to the instant claims 22, Jou et al. teach that first and second probe differs by a single nucleotide (see page 10, lines 5-21);

With reference to the instant claims 24 and 25, Jou et al. teach that the method comprises four amplification primers (see page 15, lines 1-5); comprises less than four primers and at least one primer of the amplification primers hybridizes to both mutant and wild type sequences (see page 11, lines 1-2).

With reference to 23 and 35, Labuda et al. teach that the method is useful for altering the patient's care regimen (altering metabolism of drugs and /or altering cancer susceptibility) (see page 85, column 1, paragraph 1).

With reference to the instant claims 28- 32, 36-37, the method comprises labeling of primers and probes (see page 7, lines 3-13).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting a variant (CYP2D6 gene deletion) as taught by Johansson et al. with a method for detection of amplification product as taught by Jou et al. to achieve expected advantage of developing a method for enhanced

sensitivity of detecting a target nucleic acid and its variant because Johansson et al. states that "it was considered of importance to develop simple PCR-based methods that could be used for efficient genotype analysis of ultrapid metabolizers" (see page 351, column 2, lines 15-18). One such alternative favoring efficiency, expressly motivated by Jou et al. is to use porbe(s) in PCR based amplification detection of target. An ordinary practitioner would have been motivated to combine the method of Johansson et al. with the method of Jou et al. in order to achieve the expected advantage of developing a sensitive method for amplification based detection of target nucleic acid.

b. Claims 10-16, 23, 26-27, 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansson et al. (pharmacogenetics, vol. 6, pages 351-355, 1996) and in view of Labuda et al. (Anal Biochem., Vol. 275: 84-92, 1999).

Johansson et al. teach a method for distinguishing the presence of a target nucleic acid and a variant which comprises a deletion (deletion of entire coding region (CYP2D6*5)), wherein Johansson et al. disclose that the method comprises contacting a test sample (containing DNA) with amplification reagents and a first and second amplification primer specific for the target site, subjecting the reaction mixture to amplification conditions, and detecting the amplification product as an indication of the presence of the target nucleic acid sequence (see page 351, column 1, paragraph 1, and page 353, column 2, paragraph 1). Johansson et al. also teach that (i) the method comprises control nucleic acid and primers to amplify control nucleic acid sequences, which could be selected from the said first and second primers (see page 354, column 1, paragraph 2); (ii) failure to detect an amplification product is an indication of the presence of the variant (CYP2D6 gene deletion) in the sample (see page 354, column 1,

paragraph 2); the method could be used to alter drug therapy (patient's care) and for evaluating the linkage between the CYP2D6 genotype and disease and aid in drug development (see page 354, column 2, paragraph 1). However, Johansson et al. did not teach amplification of multiplex polymerase chain reaction (PCR) for amplifying more than two alleles at a given time.

With reference to the instant claims 10, 26-27, Labuda et al. teach multiplex PCR method, wherein Labuda discloses that the method comprises amplification of more than one target nucleic acids in the same amplification reaction mixture comprising additional primers, and detection of each amplified target (see page 86, column 2, paragraph 2, page 87, column 1, paragraph 1, column 2, paragraph 1).

With reference to claims 14-16, 33-34, Labuda et al. teach a method for amplification of CYP2D family polymorphic variants including CYP2D6 * 3 (1-bp deletion), CYP2D6 * 4 (see page 84, column 1, paragraph 1 (abstract), 85, Fig 1B, page 86, table 1, column 2, paragraph 2);

With reference to the instant claims 28, and 31, Labuda et al. teach detection of amplification products using hybridization with labeled allele specific probes (see page 87, column 2, paragraph 1, page 88, column 1, lines 1-14, column 2, lines 1-5);

With reference to claims 23, and 35, Labuda et al. teaches that the method is useful for altering the patient's medical care regimen (altering metabolism of drugs and / or altering cancer susceptibility) (see page 85, column 1, paragraph 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting a variant as taught by Jou et al. with a method for amplification of CYP2D6 using multiplex PCR as taught by Labuda et al. to achieve expected advantage of developing a method for enhanced sensitivity of detecting a target

nucleic acid and its variant because Johansson et al. states that "the entire CYP2D6 gene can be used as template for appropriate allele-specific PCR amplifications. Genotyping for the four most common defect variants (CYP2D6 * 3, CYP2D6*4, CYP2D6*5 and CYP2D6* 6) will yield in most cases about 90-95% predictability for the debrisoquine PM phenotype" (see page 354, column 1, paragraph 2) .One such alternative favoring allele-specific genotyping, expressly motivated by Labuda et al. is to use multiplex PCR for amplifying more than one target. An ordinary practitioner would have been motivated to combine the method of Johansson et al. with the method of Labuda et al. in order to achieve the expected advantage of developing a sensitive method for amplification based detection of polymorphic variants of a target nucleic acid.

No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru

June 14, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER